

Mitochondrial disorder caused Charles Darwin's cyclic vomiting syndrome

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Background: Charles Darwin (CD), “father of modern biology,” suffered from multisystem illness from early adulthood. The most disabling manifestation was cyclic vomiting syndrome (CVS). This study aims at finding the possible cause of CVS in CD.

Methods: A literature search using the PubMed database was carried out, and CD's complaints, as reported in his personal writings and those of his relatives, friends, colleagues, biographers, were compared with various manifestations of mitochondrial disorders (MIDs), known to cause CVS, described in the literature.

Results: Organ tissues involved in CD's disease were brain, nerves, muscles, vestibular apparatus, heart, gut, and skin. Cerebral manifestations included episodic headache, visual disturbance, episodic memory loss, periodic paralysis, hysterical crying, panic attacks, and episodes of depression. Manifestations of polyneuropathy included numbness, paresthesias, increased sweating, temperature sensitivity, and arterial hypotension. Muscular manifestations included periods of exhaustion, easy fatigability, myalgia, and muscle twitching. Cardiac manifestations included episodes of palpitations and chest pain. Gastrointestinal manifestations were CVS, dental problems, abnormal seasickness, eructation, belching, and flatulence. Dermatological manifestations included painful lips, dermatitis, eczema, and facial edema. Treatments with beneficial effects to his complaints were rest, relaxation, heat, and hydrotherapy.

Conclusion: CVS in CD was most likely due to a multisystem, nonsyndromic MID. This diagnosis is based upon the multisystem nature of his disease, the fact that CVS is most frequently the manifestation of a MID, the family history, the variable phenotypic expression between affected family members, the fact that symptoms were triggered by stress, and that only few symptoms could not be explained by a MID.

Keywords: hyperemesis, cyclic vomiting, fatigue, metabolic disease, mitochondrial disorder, multisystem disorder, respiratory chain

Introduction

Cyclic vomiting syndrome (CVS) is a rare, chronic, debilitating, functional, gastrointestinal disorder initially described in children¹ but increasingly recognized in adults.^{2,3} CVS is characterized by recurrent, stereotypic episodes of intense nausea, intractable nonbilious vomiting, and abdominal pain lasting hours or days.^{4,5} Between the attacks, patients remain symptom-free and return to baseline health, unless CVS has become coalescent.⁵ The most common prodromal symptoms are nausea and abdominal discomfort.⁶ In adults, CVS is commonly associated with anxiety and depression.⁷ Triggering factors include stroke,⁶ intake of morning medication,⁶ or cannabis abuse.⁸ Severity of CVS in adults ranges from mild disease with infrequent episodes to severe, life-disabling disease requiring multiple emergency department visits or

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frequent hospitalizations.^{9,10} Frequently, CVS is associated with migraine, particularly in children,¹¹ or mitochondrial dysfunction.¹² Onset of CVS is earlier among those who develop migraine.¹¹ In adults, CVS is frequently associated with autonomic dysfunction, more frequently with sympathetic than with parasympathetic dysfunction.¹³ Females with CVS frequently have hyperemesis during pregnancy.

CVS occurs in all age groups, with a mean age of onset of 4 years in children¹⁴ and 35 years in adults.⁵ The demographic profile and disease characteristics are similar in pediatric and adult-onset CVS; however, pediatric CVS more likely occurs in females and has a higher prevalence of concomitant neurological abnormalities.³ In a study of 101 CVS patients, 65% were female and 29% were pediatric cases.³ The prevalence of cognitive impairment is higher in children as compared to adults.³ Latency between onset and diagnosis is longer in pediatric as compared to adult patients.³ CVS is a rare condition in adults but is regarded as the second most common cause of recurrent vomiting after gastroesophageal reflux in children, affecting 1.9% of school-aged children.¹⁵ CVS is present in about 2% of Scottish and Western Australian school children.^{16,17} Despite increasing awareness, CVS often remains unrecognized for months or even years in children and adults.

The etiology is multifactorial and heterogeneous since CVS has been described in patients with mitochondrial disorders (MIDs) and fatty acid oxidation disorders (FAODs).^{4,18} In pediatric cases with migraine, CVS was associated with the mitochondrial DNA single nucleotide polymorphisms m.16519C>T and m.3010G>A.^{19–22} CVS was reported in a patient with Kearns–Sayre syndrome²³ due to a 3 kb mitochondrial DNA deletion with a heteroplasmy rate of 30%–40% in blood, and it was also a phenotypic feature in seven of eleven patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) first described in the literature.²⁴ Episodic vomiting is also a frequent feature of other MELAS patients,¹² mitochondrial neurogastrointestinal encephalomyopathy,²⁵ mitochondrial depletion syndrome due to *MPV17* or *TYMP* mutations,²⁶ Leigh-syndrome,²⁷ or nonsyndromic MIDs.²⁸ Additionally, maternal inheritance of symptoms and signs and abnormal urinary excretion of organic acid in children suggested MID to have been causative.^{29–32} Some CVS patients may also present with lactic acidosis.^{10,33} CVS has been regarded a manifestation of migraine by some authors³⁴ since it evolves to migraine in one third of the cases.^{32,35} Further arguments for a mitochondrial defect as cause of CVS are the frequent transmission of CVS via a maternal trait of inheritance,³²

the frequent association of CVS with other typical clinical manifestations of a MID,^{11,36,37} the abnormal urinary organic acid profile in some CVS patients,³² and the beneficial response of CVS to compounds such as L-carnitine or coenzyme-Q, which are frequently used as supportive measures in MIDs.¹² In a 20-year-old adult, CVS was attributed to the FAOD multiple acyl-coenzyme A dehydrogenase deficiency, manifesting with anion gap metabolic acidosis, nonketotic hypoglycemia, collapse, multiorgan failure, and death.¹⁸

Generally, CVS is diagnosed upon the history, clinical presentation, and after exclusion of other possible causes.³⁸ In adults, CVS is diagnosed according to the Rome III criteria, which include stereotypic, acute-onset episodes of nausea and vomiting lasting <1 week, more than two episodes within the previous year, and absence of nausea or vomiting between the episodes.³⁹ In children, CVS is diagnosed according to essential criteria (recurrent, severe, discrete episodes of vomiting with varying intervals of normal health between episodes) and supportive criteria (vomiting episodes and patterns which are similar to each other within each individual case).⁴⁰ Laboratory and radiographic studies are typically normal.^{32,35,40} Because of the lack of awareness, CVS is often diagnosed with delay, particularly in adults.⁵ The diagnosis may be also delayed because there is no specific test to confirm the diagnosis. In cases in which CVS remains unrecognized, patients undergo unnecessary diagnostic procedures and treatment without benefit⁴¹ and may develop interepisodic nausea and loss of periodicity (coalescence of symptoms).³ Differential diagnoses include hydrocephalus, brain tumor, Budd–Chiari malformation,⁶ medium chain acyl-CoA dehydrogenase deficiency, late-onset form of glutaric acidemia type II, short chain acyl-CoA dehydrogenase deficiency, short-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, gastrointestinal reflux, and chronic cannabis abuse.⁴ These diagnoses need to be excluded before diagnosing CVS.

There is no standard, evidence-based, generally accepted treatment of CVS.⁵ Only symptomatic measures are available, which can be separated into prophylactic measures and treatment of the acute symptoms. Prophylactic treatment is usually carried out with cyproheptadine (age ≤5 years) or amitriptyline (age >5 years). Some patients may benefit from flunarizine, a selective calcium antagonist,³⁴ and some patients additionally respond to topiramate, coenzyme-Q, or L-carnitine.³ The response rate to amitriptyline was reported as 52.7% in an open-label, subject recall-based study in children and adults.¹² The efficacy of coenzyme-Q is similar to

that of amitryptiline.¹⁴ Therapy of acute symptoms includes application of intravenous fluids with up to 10% glucose to limit ketosis.⁴² In addition to fluid resuscitation, various drugs are applied; most frequently antiemetic medication, like ondansetron, antimigrainous drugs, α -blocking agents such as dexmedetomidine or clonidine, proton-pump inhibitors, or sedatives are applied.⁵ Sartanes have also been shown to have beneficial effects in episodes of CVS.⁴³ In patients with intractable vomiting, valproate or phenobarbital may be helpful as a prophylaxis of vomiting.⁴³ Most patients report a benefit from hot bathing,⁸ which is why they spend hours in a bath or under a shower.⁴⁴ In most children, symptoms are relieved by sleep.⁴⁰ Age at onset does not predict the response to standard treatment,³ and compliance appears to be the only factor associated with a favorable response.³

One of the historic celebrities in whom CVS is suspected is Charles Darwin (CD).^{45,46} According to his own description (letters, autobiography, diary of illness), the description of his wife Emma (diary), historical witnesses (correspondence with friends, colleagues, doctors), and reports of others about his condition, he most likely suffered from CVS for years, but it is unclear if CVS in CD was due to a MID, a FAOD, or another cause. This study aims at finding out which of the possible causes of CVS could have been responsible for CD's symptoms.

Materials and methods

A literature search using the PubMed database was carried out, and CD's complaints, as reported in his diary, his correspondence with friends, colleagues, his doctors, or in his diary of illness, and in the descriptions by his wife, children, colleagues, the writings of his doctors and biographers were compared with various manifestations of MIDs or FAODs described in the literature.

Results

Biography of CD

CD was born on February 2, 1809 as the fifth child to Robert Darwin and Susannah Wedgwood. Susannah had two sisters (Mary Anne, Sarah) and three brothers (Josiah, Richard, Tom) (Figure 1). CD was brought up in Shrewsbury, where he also went to school (Table 1). In October 1825, CD started to study medicine in Edinburgh but gave up his medical studies after 2 years to switch to theology in Cambridge in January 1828 (Table 1). After graduation from Cambridge, he was selected to participate in an expedition aboard the ship "Beagle" to South America and around the world. This expedition lasted 5 years, from December 1831 to October 1836, and provided

the basis for his theories on human evolution and sexual selection. After his return, he relocated to London in March 1837. In January 1839 CD married his first cousin Emma, who bore him ten children between 1843 and 1856, seven of which survived into adulthood (Henrietta, George Howard, Elizabeth, Francis, Leonard, Horace, Charles) (Figure 1). In 1842 the Darwins moved to Downe, Kent, south of London. Since his return from the expedition, he had started extensive experimental and publicatory activities. Between 1858 and 1859 he wrote a short version of the "*Origin of Species*." He also became closely involved in the activities of national scientific societies and held several official positions. Along with his scientific passions, he engaged with many of his national and international colleagues and combatants and gained international reputation and increased attention. However, most of his activities were frequently interrupted by a chronic, episodic, slowly progressive illness that forced him to reduce or stop his work for days or weeks and lastly resulted in social retreat. Despite these restrictions and limitations, he continued his pioneering and inspiring work and correspondence and further developed his revolutionary theories on evolution until his older years. He died in April 1882 at the age of 73 years, most likely from myocardial infarction during an episode of his illness.

Medical history

Contrary to his celebrity for his scientific merits, CD is hardly known for the disease he suffered from since adolescence throughout the rest of his life. In recent years however, his illness has gained attention, and an increasing amount of literature has been published on this topic.^{45–50} His medical history is noteworthy for dyslexia and amusia, and at school-age in Shrewsbury he developed prominent flatulence, which is why he was given the nickname "gas" (Table 2).⁵¹ During his time as a student in Edinburgh and Cambridge he developed periodic nausea, retching, and bilious vomiting, occasionally with clots of blood (hematemesis). These symptoms were associated with bloating and abdominal pain.⁵² He vomited 2–3 hours after eating but did not vomit food, which is why he did not lose weight. Initially, he seemed to have been an athletic young male, but at age 20 years, he first reported intense fatigue and lethargy after attending two music concerts within one day.⁵³ During the 5-year circumnavigation aboard the "Beagle," he was affected by intense seasickness, which became worse as the voyage progressed. Occasionally, CD was also sick when ashore. During land excursions he sometimes developed tiredness, fatigue, general weakness, lethargy, and exhaustion, giving him the feeling of being

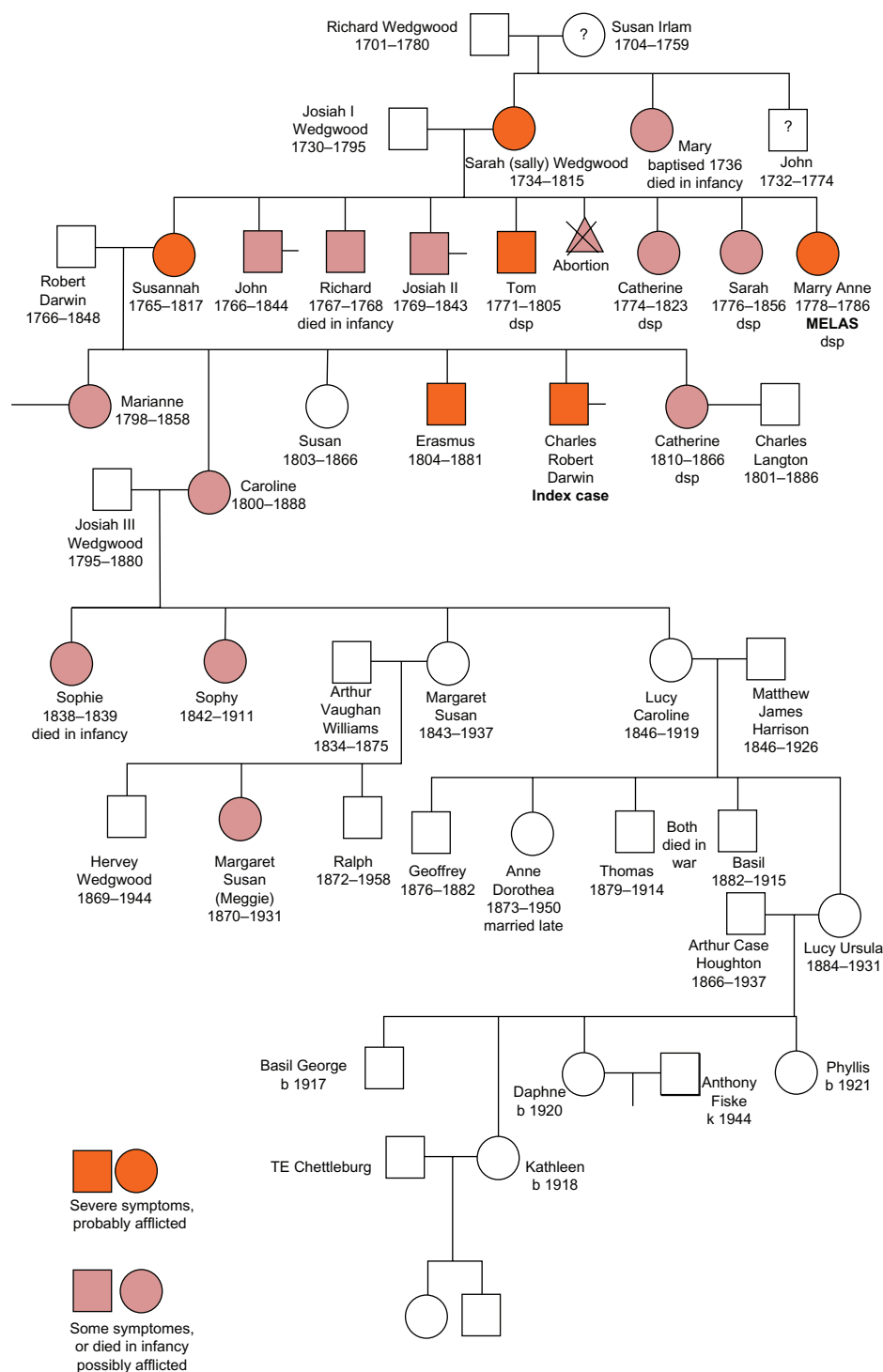


Figure 1 Family tree of Charles Darwin's (CD) relatives.

Notes: First Generation: Susan Irlam, who died relatively young (55 years), had three children. John, who died suddenly at age 42 years; Mary, who died in infancy; and Sarah, the mother of Susannah and grandmother of CD, who developed chronic illness.

Second Generation: John Wedgwood died suddenly, aged 42 years, "stricken with a severe illness." He was seen by Dr Erasmus Darwin but "nothing could be done." A sudden, severe illness, causing death after a week or so would be consistent with acute pancreatitis and peritonitis. Sarah (Sally) Wedgwood, wife of Josiah (Josiah I) Wedgwood, mother of Susannah and grandmother of CD, was healthy and active when young, but she developed chronic illness with severe arthritis and "rheumatism." Some of her symptoms are those of the condition known today as fibromyalgia. In addition to her eight children, all of whom had evidence of hereditary disease, she had serious illness after a miscarriage. This illness was diagnosed by Dr Erasmus Darwin as "inflammation of the liver," most likely an acute fatty liver. Mary Wedgwood died in 1736, the year of her baptism. British Genealogy¹⁰⁸ states that she had died in the year of her birth. The widowed Richard Wedgwood is reported as having two children only.

Third Generation: Susannah (Sukey, Susan) Darwin, CD's mother, had a history of vomiting and boils as a child and later had "difficulties" with pregnancies, which was probably hyperemesis. Famously "never quite well and never very ill" and "everyone seems young but me." She had a history of motion sickness, and died with sudden, severe abdominal illness and probable acute hemorrhagic peritonitis, an illness similar to that of her maternal uncle John. John suffered from (essential?) tremor all his life.

(Continued)

Essential tremor may occur in association with dysautonomia; both CD and his maternal uncle, Tom, had evidence of dysautonomia. Richard died in infancy with an "acute abdominal complaint" suggesting acute pancreatitis. Josiah II, developed Parkinson's disease in later life. Tom, suffered headaches and abdominal pains even as a student. He also had periods of lethargy, periodic vomiting, suffered severe seasickness, had heat and cold intolerance, became addicted to opium, and died by opium over-dosage at the age of 34 years. Catherine "Kitty" described as "somewhat masculine" and the least attractive of the adult sisters, developed an abdominal tumor that reached an immense size. Her masculine appearance suggests that she may have had polycystic ovaries or the Stein–Leventhal syndrome, the most common cause of such endocrine effects in females. Patients with this syndrome may develop cystic ovarian tumors that, if untreated, may become very large. Sarah had no history of illness, but in the one portrait of the family she is depicted as having ocular hypertelorism. She never married, but she was apparently attractive and declined several proposals of marriage. Mary Anne was of short stature and had physical and intellectual disabilities. She suffered headaches, fits, periods of paralysis and blindness, and she progressively declined until death at the age of 8 years.

Fourth Generation: Marianne Parker, CD's eldest sister, married Dr Henry Parker in 1824. Even before her marriage she had a reputation for irritability: "... of course you know how peevish Maryane (Marianne) is when she is unwell." The Parkers had five children, four boys and a girl. There is no record of living female line descendants of any of these children. Marianne died in 1858, at the relatively young age of 60 years, 2 years after her husband. "We have just heard of my sisters Marianne Parker's death, – a blessed relief after long continued and latterly very severe suffering." No detailed description of her sufferings has been found but it is possible she experienced symptoms that today would be called fibromyalgia. Caroline Wedgwood married her first cousin, Josiah III. They had four daughters; the first died in infancy. She had a prolonged period of mental illness that lasted for 12 years. Emma, Charles' wife, writing to her daughter Henrietta, described her:

[...] looking so ill and depressed. Her health is so bad and she feels so desponding about her life and feels so utterly unable to reconcile herself to the loss of Margaret (a daughter who married) [...]. She has grown so immensely large and feels so great a figure that she can hardly bear to go anywhere.⁹⁰

Caroline became careless in her appearance and forgetful of even the simplest details of managing a household and a family. She recovered from this period of severe illness but was always described as being "eccentric" and "secretive." In her old age she was severely handicapped with arthritis. Susan Darwin, the surrogate mother of the family after Susannah's death, was the mistress of the household, the keeper of accounts, the schoolmistress who corrected Charles' spelling, and as well, the generous aunt who brought up Marianne's five children after her death in 1858. She never married or had any children of her own and died only a few months after her younger sister Catherine. Although she died at the relatively young age of 63 years, there is no record of her having had illness. Erasmus Alvey Darwin, CD's elder brother was described as having "rheumatism" at an early age and being very pale and was regarded as a chronic invalid throughout his adult life. CD wrote: "All my sisters are well, except Mrs Parker, who is much out of health; and so is Erasmus at his poor average." In later life he had episodic attacks of pain and nausea. CD noted of his brother: "He takes no wine or smoke, but sticks to his opium with many groans." Erasmus died in August 1881 at the age of 76 years. Catherine Langton married Charles Langton, a widower, in 1863 at the age of 53 years. Like her mother before her and two of her older sisters, Catherine was never "completely well," and at the time of her marriage she was described as being "in poor health" and having a "depressive disposition." When she died, CD wrote to Hooker: "Poor thing she suffers much." She never had children.

Fifth Generation: Initial searches have found little record of Marianne Parker's five children, four boys and one girl, particularly no history of illness. The four boys were pallbearers at their grandfather's (Dr Robert Darwin's) funeral, a funeral that CD was unable to attend due to illness. The one daughter, 17-year-old Mary Susan Parker, was described by CD: "who though dull is a nice girl." She married Major Edward Mostyn-Owen and had two daughters and three sons. Maud Mostyn-Owen died at the age of 18 years, and there is no record of her having children. No record of Henrietta Susan Mostyn-Owen has been found. Sophie Wedgwood died in infancy. Sophy Wedgwood, Caroline's eldest surviving daughter, never married and became a recluse after her mother died. Even before this, Emma, CD's wife, noted: "poor Sophy strikes one anew every time one sees her as utterly dead and quite as much dead to mother and sisters as to outsiders." She is recorded as becoming very miserly, serving guests at a dinner party with a single orange, secreting food in corners throughout her house, and searching rubbish bins for scraps that she considered of value. Margaret Wedgwood, Caroline's second surviving daughter, married Arthur Vaughan Williams. There is no record of Margaret having illness, and she helped her sickly elder sister, Sophy, nurse their dying mother. Their younger son, Ralph Vaughan Williams (1872–1958), became a famous composer, and was assisted in his music work by his older sister Margaret Susan (Meggie). Meggie, although vivacious and talented early in life, developed marked cognitive decline and spent the last decade of her life in a vegetative state. The older son, Hervey Wedgwood, is known to have married but no other details have been found. Lucy, Caroline's third surviving daughter, married Matthew James Harrison, and they had three sons and two daughters. Lucy migrated with her husband to Canada where she died. No record of illness in herself, her children, or her children's children has been found.

Abbreviations: b, born; dsp, decessit sine prole (died without issue); k, killed; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

"knocked-up" (Table 2). Additionally, attacks of headache and visual disturbance occurred and were of such a severity that they incapacitated him for days (Table 2).⁵¹ During the years after his return from the expedition, he still suffered from episodic nausea, retching, vomiting, palpitations, episodes of panic, and headache.⁵⁴

His attacks could be triggered by stressful events, excitement, pleasurable events, anxiety, infections, exposure to heat (in South America), or exposure to cold. Even the birth of his first child (Erasmus) in 1839 caused severe headache before the birth and a "knocked-up" state after delivery.⁵⁵ Because of early exhaustion, CD increasingly retreated from visiting friends, joining parties, or inviting colleagues during his stay in London. During 1840 CD's illness worsened, and he developed eructation.⁵⁶ At the same time he started to complain about temporary numbness of all his fingers.⁵⁷ After having moved to Downe, south of London in 1842, the Darwins returned into society, but his health almost always suffered from the excitement with attacks of violent shivering and vomiting (Table 2).⁵⁸ For this reason, he gave up all

dinner parties and when scheduling a meeting with friends or colleagues, he warned them in advance that he might fail to come because of his uncertain health.⁵⁹ In 1845 he realized that he could no longer attend meetings,⁶⁰ and since 1848, he reported eye symptoms such as fiery spikes or dark clouds before the eyes. In 1848 he experienced a first episode of depression. His illness further progressed such that he could not even attend his father's funeral in November 1849.⁶¹ In 1852 he complained that even day trips to London brought on fatigue. Traveling to Sydenham in 1854 to watch the opening of the new Crystal palace by Queen Victoria again resulted in sickness and headache.

Since 1849 he repeatedly underwent hydrotherapy at Dr James Manby Gully's institute at Malvern with a beneficial effect.^{62–64} In 1860 he should have attended a meeting of the British Association for the Advancement of Science in Oxford to defend his theory but could not do so because of another episode of nausea, vomiting, and headache.⁶⁵ In 1861 CD could not attend the funeral of his mentor John Stevens Henslow, and in 1862 he gave a talk at the Linnean Society

Table 1 Benchmark data of Charles Darwin's biography

Date	Event
February 12, 1809	Birth
Boyhood	School in Shrewsbury
October 1825	Start of medical studies in Edinburgh
Summer 1826	Climbs Mt. Snowdon without problems
January 1828	Starts theology studies at Cambridge
December 1831	Start of the expedition with the "Beagle"
January 1832	Praia, Cape Verde islands
February 1832	Salvador de Bahia, Brasil
December 1832	Fireland
April–November 1833	Excursions to Uruguay and Argentina
July 1834	Valparaiso, Chile
September 1835	Galapagos islands
November 1835	Tahiti
January 1836	Sidney
May 1836	Kapstadt
October 1836	Return from the 5-year expedition
March 1837	Residence in London
January 1839	Marriage to Emma, his first cousin
November 1842	Residence in Downe, London south
1849	Hydrotherapy in Malvern
April 1851	Death of his favorite daughter Annie
November 1859	Publication of "On the origin of Species....."
July 1858	Presentation of the theory of evolution at the Linnean society
June 1860	Session of the "British Assc for the Advancement of Science"
January 1868	Publication of his book "The Variation of Animals and Plants under Domestication"
1871	Publication of his book "The Descent of Man, and Selection in Relation to Sex"
1872	Publication of his book "On the Expression of the Emotions in Man and Animals"
April 19, 1882, 4 pm	Death

in London, which triggered another episode of vomiting and headache. During the same year he experienced a relapse of his skin problems (eczema, facial edema).⁶⁶ In summer of 1863 CD lost his memory for the first time, which was interpreted by his family as epileptic seizure.⁶⁷ In 1864 he was incapacitated for months because of nausea and vomiting.^{68,69} An ice bag therapy (application of ice to the skin) in 1865 was ineffective.⁷⁰ In 1867 he experienced two episodes of short-term paralysis, inability to speak, and memory loss. In 1869 CD's health improved transiently, allowing him to travel and to attend meetings but nausea, flatulence, and colics remained constant.⁶⁵ In 1875 he failed to attend the funeral of his friend Charles Lyell. His last three years of life were dominated by increasing tiredness, chest pain, and an irregular pulse (atrial fibrillation?).⁷¹ For his shivering and nonresistance to cold, fires in the grates were kept burning all year long in his home.⁵¹ CD suffered from caries and tooth decay, possibly due to his high sugar diet (he was fond of

Table 2 Onset of Charles Darwin's clinical manifestations, including those suggestive of mitochondrial disorder

Symptom	Onset	Typical MID feature	Reference
Clear onset			
Dyslexia	Boyhood	Yes	51
Scarlet fever	9 years	No	47
Flatulence	Boyhood	Yes	58,65
Painful lips, eczema	19 years	No	65,81,82
Periodic nausea, vomiting	20 years	Yes	55,60,65,69
Fatigue, lethargy	20 years	Yes	43
Abnormal seasickness	22 years	Yes	58
Palpitations	22 years	Yes	58,83,84
Faintness, sinking feeling	23 years	Yes	
Exercise intolerance	23 years	Yes	58
Headache	23 years	Yes	55,85–87
Panic attacks, fear	29 years	No	58
Overtiredness	30 years	Yes	88,89
Exhaustion	30 years	Yes	90
Eructation, belching	31 years	Yes	91
Muscle weakness	33 years	Yes	58
Fatigue	43 years	Yes	53,55,64
Prostration	49 years	Yes	92
Loss of memory	54 years	Yes	67
Myalgia	55 years	Yes	93
Atrial fibrillation	63 years	Yes	51
Unclear onset			
Finger numbness	Uk	Yes	57,66
Dental problems	Uk	No	51
Tan skin (hyperpigmentation)	Uk	No	51
Transient weakness	Uk	Yes	51
Bloating, abdominal pain	Uk	No	51
Dizziness, whizzing, swimming head	Uk	Yes	51
Muscle twitching	Uk	Yes	51
Sweating, temperature sensitivity	Uk	Yes	51
Muscle weakness	Uk	Yes	51
Visual disturbances	Uk	Yes	51
Edema of face, arm, knee, leg	Uk	Yes	51
Lumbago	Uk	No	51
Speech arrest	Uk	Yes	51
Depression	Uk	Yes	51
Tight chest, dyspnea	Uk	Yes	51
Recurrent boils	Uk	No	51
Hematemesis	Uk	No	51
Chest pain, death	73 years		
April 19, 1882 from myocardial infarction			

Abbreviations: MID, mitochondrial disorder; Uk, unknown.

pudding) but possibly also for his cyclic vomiting. He also suffered from recurrent episodes of boils, and skin abscesses due to staphylococcus infection.⁷² CD's death was associated with chest pain and dyspnea during one of his episodes, most likely from myocardial infarction or acute heart failure, but

it cannot be excluded that chest pain was due to esophagitis, gastroesophageal reflux, Barrett's esophagus, or a perforating peptic ulcer.⁴⁷

Family history

The youngest sister of CD's mother (Mary Anne Wedgwood) was of short stature, displayed physical and mental disabilities, had experienced recurrent seizures followed by partial weakness (Todd's paresis), and episodes of blindness. She died with progressive dementia at the age of 8 years (Figure 1).⁷³ The sister of Mary Anne (Sarah) presented with clear hypertelorism as can be determined from available photographs. One brother of the mother (Josiah) developed late-onset parkinsonism, and one brother (Richard) died suddenly in infancy (Figure 1). Another of CD's uncles (Tom Wedgwood) had headaches as a student and later developed severe abdominal pain, such that he "rolled around the floor in agony."⁴⁷ Like CD, he suffered from abnormal seasickness.⁷³ He died from an opium overdose at the age of 34 years. CD's mother was "never quite well."⁷³ As a child she suffered from vomiting and boils. She had difficulties with her pregnancies, spending much time in bed, which was most likely a result of hyperemesis gravidarum. She experienced motion sickness and complained about not looking young.⁴¹ After graduation, Erasmus (CD's brother) spent a life as a socialite and chronic invalid.⁷⁴ He as well suffered from abdominal pain and lethargy. CD's sister Caroline experienced "social and cognitive deterioration," and the oldest sister Marianne was described as "irritable" (Figure 1). Among CD's children, one died in infancy, one at juvenile age, and another one also at juvenile age. The surviving children suffered from frequent infections. CD's father was obese but there are no records of him having had illness. There is also no information regarding sickness of CD's father's sisters or brothers. The parents of CD's father seemed to have been unaffected as well. There are not enough data available for CD's father's side of the family to perform quantitative pedigree analysis.

Discussion

In reviewing the literature relevant to CD's illness, we have determined that MID is the most likely cause of his pleomorphic abnormalities. Despite a large number of possible differentials, his complaints were attributed to a MID because of the wide range of manifestations, the episodic nature of his complaints, the noteworthy family history, the phenotypic heterogeneity between affected family members, the triggering effect of stress or meals, and the beneficial effect of hydrotherapy and heat.

Arguments supporting CVS in CD are that he had developed periodic nausea and vomiting since his times as a student in Edinburgh and Cambridge, and the adult onset of CVS remained a severely compromising condition throughout his life. His CVS episodes increased in severity and duration with increasing age and bound him to bed for days or weeks, as in most CVS cases. A further argument for CVS in CD is the development of abnormal seasickness. Though not previously reported, the concurrence of CVS and seasickness suggests a pathogenetic link, and CVS was most likely the cause of abnormal seasickness. Abnormal seasickness bound CD to his hammock on the "Beagle" for days. The fact that he was quite fit during some land excursions on the expedition does not exclude CVS. A further argument for CVS in CD is his dental problem, a frequent finding in CVS patients, which is more likely due to damage from gastric acids rather than to his preference for sweets. The intermittent nature of CD's symptoms is also compatible with CVS.⁴⁷ A further argument for CVS in CD is his beneficial reaction to hydrotherapy. "Water cure" was the only treatment that brought CD any relief,^{45,46} and likewise, CVS patients spend hours in a bath or under a shower.¹⁶ No other treatment before or afterward was effective. Hydrotherapy has not been previously reported to have a beneficial effect on CVS, but cannabinoid hyperemesis syndrome responded favorably to compulsive hot baths.⁷⁵ Paradoxically, cannabis is predominantly known for its antiemetic properties.⁷⁶ Only in cases of chronic abuse, hyperemesis may evolve, which is why chronic cannabis abuse should be included in the differential diagnoses of CVS.⁷⁶⁻⁷⁸ A further indication for a relation between cannabinoids and emesis is the fact that low levels of endocannabinoids are associated with motion sickness.⁷⁹ Arguments against CVS in CD are that he did not recover completely after a CVS episode and that he improved only partially during warm weather conditions, as with most other CVS patients.

Several arguments for MID as the common cause of CD's complaints can be raised. The strongest argument is the wide range of organ involvement (brain, muscles, peripheral nerves, ears, heart, gut, skin). Multiorgan involvement included cerebral manifestations (episodes of weakness, episodes of memory loss, dyslexia, dizziness, presyncope, faintness, headache, panic attacks), muscular manifestations (exercise intolerance, overtiredness, exhaustion, prostration, easy fatigability, myalgia, muscle twitching), manifestations of peripheral nerves including autonomic fibers (polyneuropathy with hypoesthesia and dysesthesia in a glove-type distribution, increased sweating, temperature sensitivity,

dysautonomia), vestibular manifestations, cardiac manifestations (palpitations, probably atrial fibrillation, chest pain), gastrointestinal manifestations (CVS, dental problems, abnormal seasickness, eructation, belching, flatulence), and dermatological manifestations (painful lips, dermatitis, eczema, occasional edema of the face) (Table 2). A second argument for MID in CD is the fact that episodes of CVS could be triggered by physical stress.⁴⁷ A third argument is the family history indicating that at least one member (sister of CD's mother [Mary Anne]) suffered from a MID. Other family members presumably affected by a MID were the siblings Erasmus and Caroline, the mother and her siblings Sarah, Josiah, Richard, and Tom (Figure 1). The clinical manifestations of these family members were highly variable. Only a few of CD's symptoms do not fit with the diagnosis of a MID (Table 2).

Alternative explanations for CD's various symptoms are listed in Table 3. Transient weakness might not only be due to stroke-like episodes, seizures, or arrhythmias but may also be due to a cerebral vascular problem. Transient weakness could be due to carotid artery stenosis or intracranial artery stenosis. This arterial occlusive disease could be a manifestation of atherosclerosis, which itself may be a manifestation of a MID.⁸⁰ It is also conceivable that transient weakness represents a transitory ischemic attack due to cardiac low output failure, but it is questionable if CD ever experienced heart failure, arterial hypotension, or autonomic disturbances leading to low output failure. An argument against a stroke-like episode is that these usually last for weeks or months and are frequently associated with convulsive seizures. An argument against the presence of epilepsy is that convulsions, tongue bites, or secessus were never reported. Fatigue might be simply the consequence of the recurrent electrolyte disturbances and alkalosis from CVS. There are a number of FAODs associated with vomiting including very long chain acyl-CoA dehydrogenase deficiency, medium chain acyl-CoA dehydrogenase deficiency, multiple acyl-CoA dehydrogenase deficiency, short-chain acyl-CoA dehydrogenase deficiency, short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency, or carnitine palmitoyl transferase-1 deficiency. Arguments against FAODs, however, are that these disorders usually follow a more severe course (eg, sudden cardiac death), may be associated with rhabdomyolysis or myoglobinuria, do not follow a maternal trait of inheritance, and do not respond to hydrotherapy.

There are several reasons why it is unlikely that the differential diagnoses listed in Table 3 were the cause of CD's illness. First, it is obvious that CD suffered from a hereditary

Table 3 Differential diagnoses that have been proposed for Charles Darwin's illness

Causes	Reference
Psychiatric causes	
Reaction to birth trauma	51
Psychiatric disease	50
Neurosis	48
Hypomania	49
Depression	49
Hypochondria	47,94
Bereavement syndrome	47
Panic disorder	95
Anxiety disorder, agoraphobia	51,96
Neurasthenia	97
Nervous indigestion	98
Somatization disorder	51
Obsessive compulsive disorder	51
Repressed hatred towards father	51
Device for father-son bonding	51
Repressed hostility towards his wife	51
Unexpressed grief for loss of mother	51
Repressed anxiety over evolution	51
Conflict with religious beliefs	51
Repressed homosexual attraction to Fitzroy R	51
Malingering (shamming)	51
Central nervous system disease	
Narcolepsy	99
Ocular disease	
Chronic eye strain	100
Otologic	
Meniere's disease	51
Heart disease	
Heart disease	98
Atrial fibrillation	101
Gastro-intestinal disorder	
Irritable bowel syndrome	101
Celiac disease	47
Helicobacter infection	
Crohn's disease	101
Peptic ulcer	101
Biliary tract disease, chronic cholecystitis	48,101
Chronic appendicitis	48
Duodenal ulcer	48
Diaphragmatic hernia	102
Metabolic disease	
Mitochondrial disorder	51
Intermittent porphyria	103
Metabolic disease	104
Gout	70
Hyperinsulinism	71
Infection	
Chagas disease	50
Amoeba infection	48
Brucellosis	105
Chilean fever	48
Typhoid fever	47
Smoldering hepatitis	48
Borreliosis	51
Malaria	51

(Continued)

Table 3 (Continued)

Causes	Source
Pyorrhoea with septicemia	48
Helicobacter pylori infection	52
Candida overload	52
Intoxication	
Arsenic poisoning	47
Bismuth	47
Amyl nitrite	47
Quinine	47
Calomel (mercury)	47
Morphium	47
Exposure to preservative chemicals	51
Allergy	
Multiple allergies	47
Allergy	106
Pigeon allergy	48
Autoimmune	
Systemic lupus erythematosus	51
Blood	
Pyroluria	51
Others	
Lactose intolerance	107

disease, which is supported by the family history, showing not only affection of several family members but also similarities between the different individual phenotypes. Assuming that his disease was hereditary, infections, intoxications, autoimmune disease, or allergies could not have been causative. Second, none of the causes listed in Table 3 could sufficiently explain all manifestations occurring in CD and other affected family members. Though some of the clinical manifestations could be attributed to these differentials, MID remains the most suitable cause to explain the array of abnormalities by a common diagnosis. Transmission of CD's MID most likely follows an autosomal dominant trait of inheritance, why the mutated gene most likely locates in the nuclear DNA. Third, the transient, episodic nature of CD's complaints excludes many of the differentials listed in Table 3. The episodic nature of the complaints is typical for CVS and a number of other syndromic or nonsyndromic MIDs. Fourth, the only beneficial therapeutic effect on CD's symptoms could be achieved with hydrotherapy. Hardly any of the differentials listed in Table 3 respond markedly to hydrotherapy.

Conclusion

There are ample and stringent indications that CD suffered from an inherited, nonsyndromic, multisystem MID and that CVS in CD was attributable to the underlying MID. The definite diagnosis, however, remains speculative since no instrumental investigations were carried out that

could prove or disprove a MID. FAODs are rather unlikely given their presentation, course, and reaction to treatment. Investigations of living offspring of CD, including genetic studies, could further strengthen the suspicion that CD indeed suffered from a MID. Genetic investigations of CD's hairs are under way.

Author contributions

JF and JH analyzed and interpreted the historical patient data regarding CVS. JF analyzed available data with regard to their compatibility with a MID. JF and JH were major contributors in writing the manuscript. Both authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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